REMARKS

Applicants respectfully request entry of the amendments and remarks submitted herein. Applicants have herein amended independent claims 1, 22, 25, 40 and 46 to recite particular IS481 primer and probe sequences and/or particular IS1001 primer and probe sequences. Support for these amendments can be found, for example, throughout the specification and in original claims 2 and 3 and 23 and 24. Accordingly, claims 2, 3, 23 and 24, as well as non-elected claims 29-39, have been canceled without prejudice to further prosecution. In addition, Applicants have herein amended the specification to remove embedded hyperlinks and to add a Sequence Listing. No new matter has been added by these amendments.

Claims 1, 4-22, 25-28 and 40-48 are currently pending. Reconsideration of the pending application is respectfully requested.

Sequence Listing

The Examiner asserted that the present application does not meet the requirements of 37 CFR §1.821 – §1.825. According to the Examiner, the June 25, 2008 submission did not comply because no paper copy was submitted and no Verified Statement was submitted.

Applicants note that the June 25, 2008 submission was electronic. Therefore, a.txt file uploaded via EFS is sufficient and fully complies with 37 CFR §1.821 – §1.825. For the courtesy of the Examiner, Applicants submit herewith another copy of the Sequence Listing. No new matter is introduced in the attached Sequence Listing. In view of the attached Sequence Listing and the remarks herein, Applicants respectfully request that the present objection be withdrawn.

Objections to the Specification

The Examiner objected to Applicants' disclosure for containing embedded hyperlinks and/or other forms of browser-executable code.

Applicants have herein amended the specification at pages 20, 22, and 26 to remove the embedded hyperlinks. In view of this amendment, Applicants respectfully request that the objections to the specification be withdrawn.

Rejections Under 35 U.S.C. §112

Claims 8 and 20 stand rejected under 35 U.S.C. §112, second paragraph, as the Examiner asserted that those claims are indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention.

The Examiner asserted that claim 8 is indefinite over the recitation of "measuring the wavelength emitted by said acceptor fluorescent moiety." Without acquiescing to the Examiner's rejection, Applicants have herein amended claim 8 to recite measuring the intensity of light emitted by said acceptor fluorescent moiety at said wavelength. Applicants respectfully submit that a skilled artisan, upon reading the specification, would understand the metes and bounds of pending claim 8.

The Examiner asserted that there was insufficient antecedent basis in claim 20 for "said portion of said IS481 nucleic acid molecule." Applicants have herein amended claim 20 to recite "a portion" of said IS481 nucleic acid molecule.

In view of the amendments and remarks herein, Applicants respectfully request that the rejection of claims 8 and 20 under 35 U.S.C. §112, second paragraph, be withdrawn.

Rejection Under 35 U.S.C. §102

Claims 46 and 47 stand rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Van der Zee et al. (J. Clin. Microbiol. 31:2134-2140, 1993). Specifically, the Examiner alleged that Van der Zee et al. teaches PCR-based amplification with IS481-specific primers to detect the presence or absence of *B. pertussis* in a patient sample. Applicants respectfully traverse this rejection with respect to the pending claims.

Applicants have herein amended independent claim 46 to recite two specific primer sequences (SEQ ID NO:1 and SEQ ID NO:2). Van der Zee et al. neither teaches nor suggests the particular sequences recited in claim 46 and, therefore, does not anticipate present claims 46 and 47. In view of the amendments and remarks herein, Applicants respectfully request that the rejection of claims 46 and 47 under 35 U.S.C. §102(b) be withdrawn.

Rejections Under 35 U.S.C. §103

Claims 1, 4-14, 18-20, 22, 25-28 and 40-43 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Van der Zee et al. (*J. Clin. Microbiol.* 31:2134-2140, 1993) and Wittwer

et al. (U.S. Patent No. 6,174,670); claim 48 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Van der Zee et al. and Wittwer et al.; claim 2 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Van der Zee et al. and Wittwer et al., and further in view of McLafferty et al. (*J. Gen. Microbiol.*, 134: 2297-2306, 1988) and Buck et al. (*Biotechniques* 27:528-536, 1999); claims 15-17 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Van der Zee et al. and Wittwer et al., further in view of Longo et al. (*Gene* 93:125-128, 1990); claim 21 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Van der Zee et al. and Wittwer et al., and further in view of McMillan (U.S. Patent No. 6,312,929); claims 23 and 24 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Van der Zee et al. and Wittwer et al. further in view of Van der Zee et al. (*J. Bacteriol.*, 175:141-7, 1993) and Buck et al.; and claims 44 and 45 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Van der Zee et al. and Wittwer et al. further in view of Tyagi et al. (U.S. Patent No. 5,925,517).

As indicated herein, independent claims 1, 25 and 40 have been amended herein to recite at least two specific IS481 primers (e.g., from original claim 2) and two specific IS481 probes (e.g., from original claim 3). Applicants note that the Examiner indicated that claim 3 would be allowable if written in independent form, as the Examiner did not identify any teaching or suggestion of a IS481 probe having the sequence shown in SEQ ID NO:11. Because Applicants understand SEQ ID NO:11 to be novel and non-obvious, Applicants believe that independent claims 1, 25 and 40 as amended, and those claims depending therefrom, also are novel and non-obvious.

Independent claim 22 has been amended herein to incorporate the IS1001 primer sequences from original claim 23 and the IS1001 probe sequences from original claim 24. According to the Examiner, claim 22 is obvious over the combination of Van der Zee et al. (1), which detects *B. parapertussis* using real-time amplification and IS1001 sequences (that differ from the claimed sequences), Van der Zee et al. (2), which discloses the sequence of IS1001, and Buck et al., which discloses that a number of different sequencing primers were used successfully to sequence a particular target nucleic acid.

The results of Buck et al., however, were not based on amplification reactions, did not use IS481 or IS1001 nucleic acid sequences, and did not even use *Bordetella* nucleic acid sequences. Even ignoring the fact that Buck et al. does not use *Bordetella* nucleic acid as the template, an automated sequencing reaction is significantly different from, for example, a PCR

amplification reaction in which at least two oligonucleotides generally are used, or a real-time PCR amplification reaction in which at least four oligonucleotides generally are used. The results reported by Buck et al. using sequencing primers are not representative of results using different primer and probe sequences in various types of amplification reactions because, as evidenced by the following, primer design for PCR amplification and primer and probe design for real-time PCR amplification is not always predictable.

For example, the guidelines published by the University of Chicago Cancer Research Center DNA Sequencing Facility state that one should "…be aware that no set of guidelines will always accurately predict the success of a primer. Some primers may fail for no apparent reason, and primers that appear to be poor candidates may work well" (http://cancer-seqbase.uchicago.edu/primers.html). In addition to the University of Chicago DNA Sequencing Facility guidelines, Applicants provide herewith a number of peer-reviewed publications that compare different primer sets or compare the same primer set under different amplification conditions. For example:

- the Csordas et al. reference (2004, *Lett. App. Microbiol.*, 39:187-193) states that "[p]rimers originally designed for end-point PCR did not have adequate specificity or sensitivity compared with those specifically designed for real-time PCR" (see, the Abstract);
- the Elnifro et al. reference (2000, *Clin. Microbiol. Rev.*, 13:559-570) states that "[e]mpirical testing and a trial-and-error approach may have to be used when testing several primer pairs, because there are no means to predict the performance characteristics of a selected primer pair even among those that satisfy the general parameters of primer design" (see, the first full sentence at page 560);
- the Tichopad et al. reference (2004, *Mol. Cell. Probes*, 18:45-50) states that "unknown tissue-specific factors can influence amplification kinetics but this affect can be ameliorated, in part, by appropriate primer selection" (see, the Abstract); and
- the Abd-Elsalam reference (2003, *African J. Biotech.*, 2:91-95) states that "…the most critical parameter for successful PCR is the design of primers" (see, the first full paragraph at page 94).

These references support Applicants' assertion that all primers and probes are not equivalent and may not work in a real-time amplification reaction.

Applicants' arguments are consistent with the Courts' recent decisions under 35 U.S.C. §103. Under the obviousness standard recently clarified by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.* (127 S. Ct. 1727, 1742 (2007)), such evidence of unpredictability strongly argues against the Examiner's obviousness rejections. As held by the Supreme Court in *KSR*:

> When there are a *finite* number of identified, *predictable* solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the *anticipated* success, it is likely the product not of innovation but of ordinary skill and common sense (emphasis added).

Such is not the case in the present application; the "known options" in the prior art are not "finite, identified, and predictable". In addition, none of the cited references, alone or in combination, provide the "anticipated success" referred to in *KSR*. As stated by the Court in *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.* (520 F.3d 1358, 1364, 86 USPQ2d 1196 (Fed. Cir. 2008)), "this clearly is not the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness."

To further support the rejection, the Examiner asserted that the claimed primer and probe sequences represent "structural homologs" of prior art sequences, and the Examiner cited *In re Deuel* to support this assertion. That is, according to the Examiner, the IS1001 oligonucleotide sequences disclosed by Van der Zee et al. (1) are "structural homologs" of the presently claimed primer and probe sequences, even though Van der Zee et al. (1) et al. does not disclose any of the presently claimed sequences. Contrary to the Examiner's assertion, *In re Deuel* does not indicate that two oligonucleotides that have different sequences but are complementary to the same target sequence are "structural homologs." *In re Deuel* held that claimed nucleic acid sequences were not obvious over prior art references that disclosed partial amino acid sequences encoded by such nucleic acid sequences and, therefore, *In re Deuel* is not germane to claims reciting specific nucleotide sequences such as those in the present case.

In addition, *In re Deuel* does not indicate that a primer or probe sequence that is complementary to a portion of a larger sequence is a "structural homolog," and Applicants are aware of no case law that stands for the proposition that a longer sequence makes *per se* obvious specific primer and probe sequences from within that longer sequence. Applicants understand that a longer sequence can be viewed as representing a very large genus of possible sub-sequences from which appropriate primers and probes can be selected. However, based on current case law, each of the claimed primer and probe sequences is not obvious over sequences disclosed in the cited references, and the particular combinations of four sequences that are claimed are certainly not obvious over sequences disclosed in the cited references. See, for example, *In re Bell* (991, F.2d 781, 784, 26 USPQ2d 1529 (Fed. Cir. 1993)) in which the Court

held that "given the nearly infinite number of possibilities suggested by the prior art, and the failure of the cited prior art to suggest which of those possibilities [to select], the claimed sequences would not have been obvious." Further, the lack of motivation to select a particular DNA sequence from among numerous degenerate variants was a factor in determining the non-obviousness of the claims in *In re Deuel*.

As the Examiner is aware, a number of decisions, including those discussed herein, indicate that a species (e.g., a particular oligonucleotide) is not obvious over a very large genus (in this case, all possible fragments of the full-length IS1001 sequence disclosed Van der Zee et al. (2)). Applicants note that much of the case law regarding the non-obviousness of a species over the prior art teaching of a genus containing such a species (sometimes referred to as an "invention of selection") is in the chemical arts. Significantly, the Courts have stated in several major opinions that DNA is a chemical. See, for example, *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* (927 F.2d 1200, 1206, 18 USPQ2d 1016 (Fed. Cir. 1991)) in which the Court stated that "a gene is a chemical compound." As such, each of the pending independent claims recites at least four different specific chemical species.

Objective evidence of nonobviousness, which, according to *Ortho-McNeil v. Mylan* (at 1365) "is not just a cumulative or confirmatory part of the obviousness calculus but constitutes independent evidence of nonobviousness", is provided herein. For example, the sequences recited in the present claims exhibit high sensitivity and specificity toward their targets. See, for example, Examples 10 and 11 (Tables 6, 7 and 8) of Applicants' specification. In addition, each of the claimed probe sequences (SEQ ID NOs: 3, 11, 12 and 13) has a particular melting temperature that was identified and is disclosed in the specification. The particular melting temperatures can be used as confirmation of the presence or absence of *Bordetella* in a sample. Therefore, the claimed probe sequences can be used to further increase the accuracy of detecting *Bordetella*. See, for example, the paragraph bridging pages 17 and 18 and Example 5 of the specification. Thus, the exceptional sensitivity and specificity of the claimed combinations was unexpected. According to *KSR* (at 1740), 35 U.S.C. §103 does not bar patentability where, as here, the claimed invention presents an unpredictable variation of the prior art and operates in an "unexpected and fruitful manner."

In summary, Courts have long held that species (in the present case, the specific combination of oligonucleotides recited in the pending claims) are not obvious over a very large

genus (in the present case, the full-length IS1001 sequence to which the oligonucleotides have complementarity). Applicants also have provided evidence that, even after the application was filed, there was unpredictability in primer and probe design, particularly for PCR and real-time PCR reactions. Given the disclosures of both Van der Zee et al. references, one of ordinary skill in the art would not have been able to predictably modify the disclosed sequences, even in view of Buck et al., to arrive at the claimed combination of two primers and two probes having the ability to specifically amplify and detect *Bordetella* DNA by real-time PCR as do the claimed primers and probes. Further, Applicants have provided independent evidence in the form of secondary considerations that render the claims nonobvious.

None of the cited references, alone or in combination, teach or suggest the particularly claimed combination of primers and probes recited in pending claim 22. In view of the amendments and remarks herein, Applicants respectfully request that the rejection of the pending claims under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

Applicants respectfully submit that the present claims are in condition for allowance, which action is requested. Please apply any charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

/April 21, 2009/

Date:_____

/M. Angela Parsons/

M. Angela Parsons, Ph.D.
Reg. No. 44,282

Fish & Richardson P.C.
3200 RBC Plaza
60 South Sixth Street
Minneapolis, Minnesota 55402
Telephone: (612) 335-5070
Facsimile: (877) 769-7945